REMARKS

First, Applicants would like to thank Examiner J.D. Schultz for his time and helpful suggestions during the interview with Applicants representative, Cheryl H. Agris. During the interview, proposed claim amendments and the outstanding rejections were discussed.

Claims 245-255, 258 and 261 are pending in the above-referenced application. Claims 256-257 and 259-261 have been canceled. Claims 245 and 255 have been amended to more distinctly claim that which Applicants regard as their invention. Specific support is discussed below.

Claim 245 has been amended to recite that the nucleic acid sequence encoding a non-eukaryotic polymerase comprises an intron non-native to the polymerase and that the polymerase (a) is incapable of expression in an incompatible cell, wherein said incompatibility is due to failure of expression of the polymerase due to the presence of the non-native intron and (b) is capable of producing more than one copy of a nucleic acid sequence from said construct when introduced into a compatible cell. Amended claim 245 is supported by the specification on page 87, last paragraph, page 89-90, line 7 (in particular, see page 89, lines 12-22), Figure 25 and Example 19.

Claim 255 has been amended to recite that the nucleic acid construct produces a gene product comprises an intron non-native to said gene product when introduced into an incompatible cell and (a) the intron sequence is within the sequence encoding the gene product; (b) the incompatibility is due to failure of expression of said gene product due to the presence of said intron; and (c) said gene product or protein expressed from a gene product would be toxic specifically to an incompatible cell in the absence of intron. Claim 255 is supported by the specification on page 87, lines 3-14 and page 89, lines 8-13.

New claim 262 has been added to recite a specific embodiment and is directed to a nucleic acid construct which when introduced into an incompatible cell produces a gene product comprising an intron non-native to said gene product, wherein said intron sequence is within the sequence encoding said gene product and is inserted immediately 3'to (C/A)AG and said incompatibility is due to failure of expression of said

gene product due to the presence of said intron; however the intron sequence is substantially removed during processing in a compatible cell. It is supported by the specification on page 81, page 83 and page 89, lines 8-13 and Figure 24. For example on page 81, it is stated:

> The present invention provides (1) a universal composition for conditional nucleic acid processing by the introduction of a processing element into a nucleic acid sequence produced form a construct introduced into a cell. Said produced nucleic acid is processed in a compatible cel, i.e., a cell capable of processing RNA by removal of a processing element.....
>
> The present invention provides a novel method and constructs for capablility for the conditional inactivation of a gene by the use of a non-native, or heterologous, processing element which only permits gene expression in compatible cells. The method utilizes the introduction of a heterologous processing element into the coding region of a desired gene resulting in inactivation of the gene when present in a non-compatible cell. The intron can be inserted at a number sites in most genes.

As another example, on page 83, first paragraph, it is stated

> Another significant aspect of this invention concerns a nucleic acid construct which when introduced into a cell produces a nucleic acid product comprising a non native processing element which when in a compatible cell, the processing element is substantially removed during processing. The processing element can comprise an RNA processing element including but not limited to an intron....

On page 89, lines 8-13, it is stated

> The present invention (see Examples) describes the conditional inactivation of a gene (that normally does not contain a processing element(by the precise introduction of an intron between the last two G's of a site that has the post splice junction sequence (C/A)AGG.

1. The Rejections Under 35 U.S.C. §112, Second Paragraph

Claim 255 has been rejected under 35 U.S.C. §112, second paragaraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is noted that the last line of claim 255 refers to "said non-native intron". It is asserted that there is insufficient antecedent basis in the claims for this limitation because the phrase "non-native" has been canceled from the claim.

In response, claim 255 has been amended to recite "an intron non-native to said gene product". Therefore, the rejection has been overcome and should be withdrawn.

2. The Rejections Under 35 U.S.C. §112, First Paragraph

Claims 245-255, 258 and 261 have been rejected under 35 USC §112, first paragraph as failing to comply with the written description requirement. Specifically, the Office Action states

> Claim 245, and those dependent thereon are drawn to nucleic acid constructs which comprise a nucleic acid sequence that encodes a non-eukaryotic polymerase that further comprises an intron, wherein said polymerase is expressed solely in a eukaryotic cell, and wherein said polymerase is capable of producing more than one copy of a nucleic acid sequence from said construct when introduced into a cell. Applicants claim amendment of 14 October 2003 added the claim limitation pertaining to "non-eukaryotic polymerases", and "wherein said polymerase *is* expressed solely in a eukaryotic cell". However, there does not appear to be support for these claim limitations in the specification as filed, and Applicants only reference to such support alleges that the amendments "are supported by the specification"*(pg* 14 of Applicants' response). Applicants had previously disclosed and claimed only a polymerase comprising a non-native intron, but this is not considered to provide support for the phrase non-eukaryotic polymerase..-wherein said polymerase is expressed solely in a eukaryotic cell, because they are clearly different entities with non-overlapping *scope,* and thus *one* of skill would not have been led from the former to the latter.
>
> Furthermore, the same new matter issue is considered true in regards to claims *255* and 261, ". ..comprising a eukaryotic intron, which when in a eukaryotic cell, said intron is removed during processing and wherein said gene product or protein expressed from a gene product would be toxic to a non-eukaryotic cell in the absence of said non-native intron." A review of the specification as filed does not reveal support for the genus of eukaryotic inborn, *or* for the concept of toxicity to a non-eukaryotic cell in the absence of said non-native intron. Should Applicants disagree, Applicants are invited to point out with particularity by page and line number where such support may exist. In the absence of any specific indication of support (other than "throughout the specification"), These limitations are considered to comprise new matter.

Applicants respectfully traverse the rejection. However, in order to advance prosecution, claims 245 and 251 have been amended. Specifically, claim 245 now is directed to a nucleic acid sequence which encodes a non-eukaryotic polymerase which comprises an intron non-native to said polymerase; claim 245 further recites that the polymerase is incapable of expression in an incompatible cell due to the failure of expression of the polymerase due to the presence of the intron and is capable of producing more than one copy of a nucleic acid sequence form the construct when

introduced into a compatible cell. As noted above, claim 245 is supported by the specification in general on page 81 and specifically on page 87, last paragraph where it is stated

> The present invention provides utility for the inactivation, **in incompatible cells,** of the expression of polymerase catalysts whose expression can be realized **in compatible cells**. This has application to expression of a variety of gene products, either RNA or protein, under control of promoters of a variety of polymerases. Polymerases, native and non-native to the cell, that could be used in this way include RNA polymerases from T3, T7 and SP6.

Further support is provided on page 89 where it is stated:

> In an application of the present invention, an intron is introduced into the coding sequence of T7 RNA polymerase in a construct that also contains a T7 promoter directing the transcription of a useful gene product.....The present invention (see Examples) describes the **conditional inactivation of a gene (that normally does not contain a processing element) by the precise introduction of an intron between the last two G's of a site that has the post splice junction sequence (C/A)AGG.....Therefore, a construct with this modification should lack any expression of T7 polymerase in an *E. coli* cell, but the normal coding sequence can be restored from transcripts after introduction into a compatible cell.**
>
> Applicants note that T7, T3 and SP6 polymerases would be considered to be non-eukaryotic polymerases. *E. coli* would be an example of an incompatible cell. Figure 24A show the intron insertion site; Figure 24C shows the introduction of a non-native intron and Figure 24E shows the reversion to the original coding sequence the intron has been removed. Figure 25 shows the construction of a T7 **eukaryotic** expression vector containing an SV40 intron. Figure 25 als has the caption "Active T7 RNA is only made in eukaryotic cells after splicing out of SV40 intron". An accompanying description is provided in Example 19 (from bottom of page 145-155). As stated on page 152, lines 8-10
>
> This particular eukaryotic vector was chosen since it had been shown previously that the RSV promoter is especially active in hematopoietic cell lines.

Amended claim 255 is now directed to a nucleic acid construct which produces **a gene product comprising an intron non-native to said gene product** when introduced into **an incompatible cell.** It is further recited that the incompatibility is due to failure of expression of the gene product due to the presence of the intron and the gene product or protein expression from said gene product would **be toxic specifically**

to an incompatible cell in the absence of said non-native intron. Applicants assert that there is support for amended claim 255. For example, page 89, lines 8-13 states

> The present invention (see Examples) describes the iconditional inactivation of a gene (that normally does not contain a processing element) by the precise introduction of an intron between the last two G's of a site that has the post splice juntion sequence (C/A)AGG.

Specifically, page 87, lines 6-13 states

> ..genes which would be impossible to clone, such as those which code for enzymes which destroy bacterial cell walls, **can be inactivated by intron insertion** and thus cloned in this form in a bacterium. **Genes coding for toxic products**, including tetanus toxin, risin, pseudomonas toxin, *E. coli* enterotoxins, cholera toxin and other plant, animal and microbial toxins, **can be inactived and maintained stably and safely in an incompatible cell and activeated to produce an untaltered gene product in a compatible cell**.

It is evident that amended claims 245 and 251 are supported by the specification. Claim 261 has been canceled. No new matter has been added. In view of amendments of claims 245 and 251, the rejections of claims 245-255, 258 and 261 under 35 U.S.C. 112, first paragraph, written description have been overcome. Therefore, Applicants respectfully request that the rejections be withdrawn.

3. The Rejection Under 35 U.S.C. §102(b)

Claims 245-249 and 252-254, have been rejected under 35 U.S.C. §102(b) as being anticipated by Faruqi et al. (Virology, (1991), l83(2), 764-8.) Specifically, the Office Action states

> The invention of the above claims *is* drawn to nucleic acid constructs which comprise a nucleic acid sequence that encodes a non-eukaryotic polymerase that further comprises an intron, wherein said polymerase is *expressed* solely in a eukaryotic cell, and wherein said polymerase is capable of producing more than one copy of *a* nucleic acid sequence from said construct when introduced into *a* cell, wherein the non-eukaryotic polymerase is selected from the group consisting of DNA polymerase, DNA polymerase, reverse transcriptase, and a combination thereof, or to the construct *of* claim245, wherein said nucleic acid produced from said construct is selected from the group consisting *of* DNA, RNA,a DNA-RNA hybrid and a DNA-RNA chimera, or a combination of the foregoing, or to the construct of claim 253, wherein said DNA or RNA comprises sense or antisense, or both.

> Faruqi et al. teaches a human hepatitis 33 virus polymerase that comprises introns. The construct of Faruqi *is a* viral construct which is taught as expressing a polymerase which then acts on the viral transcript to promote the expression *of* viral proteins, wherein said construct would comprise tRNA recognition and polymerase promoter sites.

Applicants respectfully traverses the rejection. However, in order to advance prosecution, claim 245 has been amended to recite that **the intron is non-native to said polymerase** and that the intron sequence is within the sequence encoding the polymerase. In contrast, Faruqi et al discloses a hapadnavirus polymerase containing an intron which is actually **native** to the polymerase. Therefore, amended claim 245 is not anticipated by Faruqi et al. Applicants note that claims 246-249 and 252-254 depend from claim 245 and would also not be anticipated by Faruqi et al.

In view of the above arguments and amendments, Applicants assert that the rejections under 35 U.S.C. §102(b) have been overcome. Therefore, Applicants respectfully request that the rejections be withdrawn.

Summary and Conclusions

Claims 245-255 and 258 are presented for further examination. Claims 245 and 255. Claim 262 has been added.

A petition fee to extend the response for three months is due. In the event that any further fee or fees are due, however, the U.S. Patent and Trademark Office is hereby authorized to charge the amount of any such fee to Deposit Account 05-1135, or to credit any overpayment thereto.

If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney request that he be contacted at (914) 712-0093.

11/30/05

Respectfully submitted,

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